REMARKS

Title Amendments:

The Patent Office asserts that the title invention is not descriptive because it is not clearly indicative of the invention to which claims are directed. Applicants respectfully disagree. The present invention is directed to antibodies to mammalian cell surface antigens. The title of the originally-filed application is descriptive because it recites mammalian cell surface antigens and reagents related thereto including specific antibodies. However, in order to expedite the prosecution of the instant application, Applicants have amended the title to include the specific wording as to "antibodies." No new matter has been entered by this amendment. A marked up version of the previous version of the title is attached.

Specification Amendments:

According to the Examiner's suggestion, the paragraph beginning at page 1, line 4, of the specification has been amended to include the patent number of the cited application. No new matter has been entered by this amendment. A marked up version of the previous version of the paragraph is attached.

Claim Amendments:

Applicants canceled claims 4 and 5, amended claims 1-3, 6-7, and 10 and added new claims 11-27, all without prejudice to their future prosecution. The claim amendments were made merely to correct matters of form. Accordingly, no new matter was added by way of these amendments.

The cancellation of claims 4 and 5 makes no admission regarding the patentability of this subject matter and should not be so construed. Applicants reserve the right to pursue this subject matter in this or in any other appropriate patent application.

Support for new claims 11, 12-13, and 14 may be found, for example, in the specification at page 23, line 31; page 25, lines 18-32; and page 3, lines 19-20, respectively. Support for new claims 15 and 25-27 can be found, for example, at page 16,

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first full paragraph; page 7, lines 8-11; and page 30, lines 30-37. Support for new claims 16-21 can be found, for example, at the original claims 2-9. Support for new claim 22 can be found, for example, at page 23, line 31. Support for new claims 23-24 can be found, for example, at page 25, lines 18-32. No new subject matter has been added.

A marked up version of the previous version of claims 1-3, 6-7, and 10 and a clean version of the entire set of pending claims are attached.

Claim Objections:

The objection to claim 10 has been obviated by correcting a typographical error: "4999E9" has been replaced with "499E9."

Sequence Listing:

In response to the Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence And/or Amino Acid Sequence Disclosures attached to this Office Action, Applicants submit herewith a Request to Transfer Sequence Listing under 37 C.F.R. § 1.821(e). A copy of the Notice is also enclosed.

Rejections Under 35 U.S.C. §112, second paragraph:

Claims 1-3 and 6-10 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particular point out and distinctly claim the subject matter which the applicants regard as the invention. The Examiner asserts that the term "binding fragment" in claims 1-3 and 6-10 is a relative term which renders the claim indefinite. The Examiner suggests that the claim recite "antigen binding fragment." The required changes have been made. Accordingly, the applicants submit that the rejection under 35 U.S.C.§ 112, second paragraph, should be withdrawn.

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Rejections Under 35 U.S.C. §112, first paragraph:

Enablement rejection

Claim 10 is rejected under 35 U.S.C. § 112, first paragraph for allegedly containing subject matter which was not described in the specification as to enable one skilled in the art to which it pertains to make and/or use the invention. The Office asserts that given the unpredictability of the relationship between protein structure and function, the specification fails to provide sufficient guidance for antibodies or fragments thereof as recited in claim 10 (a) and (c). The rejection is traversed for the reasons set forth below.

Under 35 U. S. C. § 112, all that is required is that the specification describe the invention in such terms as to enable a person skilled in the art to make and use the invention. Thus, the specification must teach one skilled in the art how to make and use antibodies or fragments thereof which specifically bind to a substantially pure or recombinant 499E9 polypeptide exhibiting 100% identity over a length of at least 12 contiguous amino acids to SEQ ID NO: 2, or to a fusion protein comprising 499E9 sequence. The test of enablement is whether one reasonably skilled in the art (1) could make and use the invention (2) from the disclosures in the patent coupled with information known in the art (3) without undue experimentation. In re Wands, 858 F.2d 731 (Fed. Cir. 1988); United States v. Telectronics, Inc., 857 F.2d 778 (Fed. Cir. 1988); M.P.E.P. 2164.01. The fact that experimentation may be complex does not necessarily make it undue. Massachusetts Institute of Technology v. A.B. Fortia, 774 F.2d 1104 (Fed. Cir. 1985); In re Wands, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Thus, the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, is it undue. In re Angstadt, 537 F.2d 498 (CCPA 1976).

Five references have been cited as state of the art at the time the application was filed, Colman (Research in Immunology, 1994, 145 (1): 33-36), Abaza et al. (Journal of Protein Chemistry, 1992, 11 (5): 433-444); Lederman et al. (Molecular Immunology, 1991, 28: 1171-1181); Li et al. (PNAS, 1980, 77: 3211-3214); and Ngo et al. In: The Protein Folding Problem and Tertiary Structure Prediction. 1994. Merz et al., Eds., Birkhauser, Boston, MA, pp. 433 and 492-495.

Colman, it is asserted, teaches that single amino acid changes in the antigen can effectively abolish antibody antigen binding. It is asserted that Abaza et al. teaches that single amino acid substitution outside the antigenic site on a protein effects antibody binding. Further, Lederman et al., it is asserted, teaches that single amino acid substitution in common allele abates binding of a monoclonal antibody. Additionally, it is asserted that Li et al. teaches dissociation of immunoreactivity from other biological activities when constructing analogs. Finally, it is asserted that Ngo et al. teaches that the relationship between the sequence of a protein/peptide and its tertiary structure are not well understood and are not predictable. These five references are asserted as evidencing a burden of undue experimentation on one of skill in the art, in practicing the claimed invention.

However, Applicants note that the cited prior art teaches that there is tolerance of amino acid sequence substitutions within antibody-antigen interfaces. For example, Colman discloses the conformational adaptability of antibody structures during binding of antigen and suggest that one antibody can serve to bind a number of different antigens (the last sentence of the first paragraph at page 33).

In addition, the claims of the instant invention do not require that an antibody be determined solely on the basis of a prediction of the tertiary structure and/or activity from the sequence of a protein/peptide. One of skill in the art would recognize that such a resource would potentially assist in solving a problem and thus, be a useful analytical tool. Nevertheless, Applicants note that the specification is not required to disclose the sequence of every antigen recited in the claims. A considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 8 USPQ 2d 1401, 1404 (Fed. Cir. 1988). In *in re Wands*, the court held that it was not undue experimentation to make many hybridoma clones and determine which ones secrete antibodies with the desired characteristics. In the present application, the experimentation involves making or selecting a battery of variant antigens and antibodies. Clear and adequate guidance with respect to making and selecting such antigens is provided in the present disclosure. For example, the specification teaches preparation of

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physical variants of 499E9 at pages 15-18; preparation of functional variants of 499E9 at pages 18-23; and uses at pages 33-43. The specification further provides detailed description as to amino acid sequence comparison (e.g., at page 16, first full paragraph). Therefore, a skilled artisan can readily decide whether a polypeptide exhibits 100% sequence identity over a length of at least 12 contiguous amino acids with SEQ ID NO: 2 or is a fusion protein comprising the 499E9 sequence, or prepare and/or purify such a polypeptide. Further, the specification provides considerable guidance to enable a skilled artisan to make and use the antibodies recited in claim 10 as originally filed. Methods of preparing antibodies are disclosed in the present specification, for example, at pages 23-26 and in Example 5. The specification also teaches how to use the claimed antibodies, for example, for treating autoimmune disorders, including rheumatoid arthritis (page 34, lines 16-26).

Therefore, no undue experimentation is required under *in re Wands*. Accordingly, the specification is fully enabling and can be readily practiced by one skilled in the art, and Applicants respectfully request withdrawal of this rejection.

Written description rejection

The rejection of claim 10 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such as way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention, is respectfully traversed for the reasons set forth below.

Pursuant to the Guidelines for Examination of Patent Applications under the 35 U.S.C. 112, first paragraph, "Written Description" Requirement (Federal Register 66 (4): 1099-1111; the "Guidelines"), possession may be shown in a variety of ways, including description of an actual reduction to practice and description of distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. Federal Register 66 (4), at 1104.

The present specification provides several distinguishing identifying characteristics sufficient to show that Applicants were in possession of the claimed invention. A natural

sequence 499E9, SEQ ID NO:2, is provided. The specification also provides characteristics of functional variants and physical variants of 499E9, as well as methods of preparation or purification thereof (see, for example, pages 15-23). The specification further provides detailed description as to amino acid sequence comparison (e.g., at page 16, first full paragraph). Therefore, a skilled artisan can readily decide whether a polypeptide exhibits 100% sequence identity over a length of at least 12 contiguous amino acids with SEQ ID NO: 2 or is a fusion protein comprising the 499E9 sequence, or prepare and/or purify such a polypeptide. Methods of preparing antibodies are also disclosed in the present specification, for example, at pages 23-26 and in Example 5.

Applicants also wish to point out that the USPTO has clearly rejected a *per se* rule requiring disclosure of complete sequences or limiting claims to only the sequence disclosed. The Guidelines, Federal Register 66 (4), at 1101, paragraph (9). Instead, "distinguishing identifying characteristics" are required under the Guidelines, which are adequately provided in the present application.

The present disclosure is also adequate under the applicable case law. As stated on page 5 of the Office Action, a description of a genus of polypeptide sequences may be achieved under *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, by means of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. Applicants have provided these common structural features. All the species encompassed by claim 10 contain a 100% sequence identity over a length of at least 12 contiguous amino acids with SEQ ID NO: 2. As discussed above, a skilled artisan can easily recognized these structural features according to the present specification and established art.

Accordingly, the requirement for written description is satisfied, and Applicants respectfully request withdrawal of this rejection.

Conclusions:

For the reasons set forth above, Applicants submit that the claims of this application are patentable. Reconsideration and withdrawal of the Examiner's rejections are hereby requested. Allowance of the claims of this application at an early date is earnestly solicited.

Respectfully submitted,
BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: Mary Ann Dillahunty

Mary Ann Dillahunty
Registration No. 34,576

P.O. Box 1404
Alexandria, Virginia 22313-1404
(650) 622-2300

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Attachment to Amendment and Reply to Office Action mailed January 29, 2002

Marked-up Copy

Title

ANTIBODIES TO MAMMALIAN T CELL SURFACE ANTIGEN[S: RELATED REAGENTS]

Attachment to Amendment and Reply to Office Action mailed January 29, 2002

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Page 1, Paragraph Beginning at Line 4

This application is a continuation of U.S. Application Serial No. 08/989,362, filed December 12, 1997, now U.S. Patent 6,242,586, which claims the benefit of U.S. Provisional Application No. 60/032,846, filed on December 13, 1996, the disclosure of which are incorporated by reference.

Attachment to Amendment and Reply to Office Action mailed January 29, 2002

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Claims 1-3, 6-7, and 10

1. (Amended) An isolated antibody, or antigen binding fragment thereof, that specifically binds to a 499E9 polypeptide having the amino acid sequence as shown in SEQ ID NO: 2.

2. (Amended) The antibody, or antigen binding fragment of claim 1, wherein the antibody is polyclonal.

3. (Amended) The antibody, or antigen binding fragment of claim 1, wherein the antibody is monoclonal.

6. (Amended) The antibody, or antigen binding fragment of claim 1, wherein the antibody is a 499E9 antagonist.

7. (Amended) The antibody, or antigen binding fragment of claim 6, wherein the [antibody] antigen binding fragment is a $F(ab')_2$, Fab, or F_v fragment.

10. (Amended) An isolated antibody, or antigen binding fragment thereof, that specifically binds to a polypeptide selected from the group consisting of:

a) a substantially pure or recombinant 499E9 polypeptide exhibiting 100% sequence identity over a length of at least 12 contiguous amino acids to SEQ ID NO: 2;

b) a natural sequence 499[9]E9 of SEQ ID NO:2; and

c) a fusion protein comprising 499E9 sequence.

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